REMARKS

I. Introduction

In response to the Office Action dated June 4, 2008, claim 1 has been amended and claims 7 and 8 have been added. Claims 1-8 remain in the application. Reconsideration of the application, as amended, is requested.

II. Claim Amendments

Applicants' attorney has made amendments to the claims as indicated above. These amendments were made solely for the purpose of clarifying the language of the claims, and do not introduce new matter. Support for the amendments can be found in the application as originally filed as follows.

Support for the amendment to claim 1 can be found in the specification at page 6, lines 14 to 24.

Support for new claims 7 and 8 can be found in the specification at page 6, lines 14 to 17.

III. Restriction Requirement

At page 2 of the Office Action, the requirement for restriction was made final. Applicants acknowledge the finality of the requirement, but respectfully request the Examiner consider rejoinder of withdrawn claims upon identification of allowable subject matter. Applicants will postpone cancellation of withdrawn claims until identification of allowable claims and further consideration of the common inventive concept.

IV. New Matter Rejection

At pages 2-3 of the Office Action, claims 1, 2, 5, and 6 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for containing new matter. The Office Action alleges that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Applicants traverse this rejection as the specification does in fact indicate that Applicants were in possession of the claimed invention as of the filing date of the provisional patent application. The language used in the claims as originally filed and in the portions of the specification noted by the Examiner, namely paragraph 0004, states that:

> Patients having the Taq1A (A1) allele (A1+ allelic status) are candidates for treatment with **high dose of high D2 dopamine receptor binding antipsychotics** and/or SSRIs that influence D2 dopamine receptor density. Patients lacking the Taq1A allele (A1- allelic status) are not likely to respond well to these SSRIs, and are candidates for treatment with **low dose of low D2 dopamine receptor binding or low dose high D2 dopamine receptor binding atypical antipsychotics**.

The passage cited above is correct in stating that A1+ patients are candidates for treatment with SSRIs, but incorrect in stating that this same population comprises candidates for treatment with high dose antipsychotics. One skilled in the art, when reading the specification as a whole, would readily detect the clerical error in that passage and in the claims as originally filed, the error being an inadvertent misplacement (switch) of the two phrases indicated in bold face in the above citation. As indicated in the title of the patent application, the invention provides a genetic marker of response to atypical antipsychotics and antidepressants. The skilled artisan would look to the data presented in the Examples and understand from this material that:

1. "Hyperprolactinemia has been considered an inevitable consequence of treatment with any typical antipsychotic agent." (See paragraph 0048, at page 15, lines 24-25, of the specification.) As is known in the art, antipsychotics "vary widely in their binding affinity for the D2 receptor" (para. 0049, at p. 16, l. 3). Some atypical antipsychotics, such as Clozapine and Quetiapine have a lower D2 binding affinity than dopamine and are not associated with hyperprolactinemia. Hyperprolactinemia is more commonly associated with tighter binding agents such as Risperidone and typical antipsychotics. (See remainder of para. 0049, which also provides literature citations.) Thus, the class of antipsychotics known as "typical" antipsychotic agents are known to be tight binders of the D2 receptor and associated with hyperprolactinemia. The "atypical" antipsychotic agents vary in their D2 binding affinity, from loose binders (Clozapine) to tighter binders (Risperidone). Prolactin levels observed, however, are not an accurate reflection of drug D2 occupancy (see discussion of Risperidone and Olanzapine as giving comparable D2 drug occupancy levels but differing in subsequent prolactin levels at end of para. 49).

2. "Although use of tighter binding agents is generally associated with higher prolactin levels it is a common clinical observation that there are considerable individual variations in prolactin levels induced by identical medication at a given dose." (See para. 50 at p. 16, l. 14-16.) The present invention is directed to this problem of predicting which patients will be best suited for which antipsychotic medication (para. 003 at p. 1).

3. The inventors have studied prolactin levels in A1+ and A1- patients treated with a variety of typical antipsychotics (Flupenthixol, Fluphenazine Decanoate, Zuclopenthixol, Haldon, Thioridazine, Thiothixene and Trufluperazine) and a variety of atypical antipsychotics (Clozapine, Olanzapine and Risperidone). The number of patients taking these various medications and who were included in the study is described in paragraph 0052 at page 17 of the specification.

4. The inventors' work has shown that A1+ patients, as compared to A1- patients, "have significantly higher prolactin levels when treated with a variety of antipsychotic medications", especially "when treated with the loose binding agent clozapine" (see Table 1 at page 21, and paragraph 0063 at page 22, lines 3-4). As noted in paragraph 0060 at page 20, lines 20-23, "when all the antipsychotics were considered together patients carrying the A1+ allele had a significant and about a 40% higher prolactin levels than patients carrying the A1- allele ($F(1,142) = 4.50$, $P = .036$)."

5. The inventors concluded that "optimal therapeutic effect is likely to be obtained at lower doses in A1+ schizophrenics. A1- patients may require a higher dose for maximal antipsychotic effect" (page 24, lines. 6-8). The inventors' finding that atypical antipsychotics, including clozapine, raise serum prolactin levels (especially in A1+ patients) runs counter to the hypothesis of Kapur & Seeman (2001, Am. J. Psychiatry 158:3, see "Conclusions" portion of abstract, copy provided herewith) that the fast dissociation of atypical antipsychotics from the D2 receptor permits an antipsychotic effect without prolactin elevation and other adverse side effects.

6. Allelic status of the DRD2 gene also differentiates response to a selective serotonin reuptake inhibitor (SSRI), as demonstrated in Example 3, found at pages 25-35 of the specification. More specifically, the study showed that post traumatic stress disorder (PTSD) patients with the A1 DRD2 allele showed a significant positive response to paroxetine treatment, in contrast to A1- patients.

7. As discussed in Example 4, at pages 35-50 of the specification, A1 allelic status is also associated with comorbid depression and anxiety in PTSD patients. A1+ status is strongly associated with comorbid somatic symptoms, anxiety, social dysfunction, and depression, independent of alcohol effects (para. 0110 at p. 40, l. 7-9).

All of these facts, supported by data, make it clear to the skilled artisan that A1+ patients are candidates for treatment with low dose DRD2 binding atypical antipsychotics and/or SSRIs, while A1- patients are candidates for treatment with high does DRD2 binding antipsychotics or alternative antidepressant. Moreover, the error of suggesting A1+ patients are candidates for

treatment with high dose high DRD2 binding atypical antipsychotics (as stated in paragraph 0004) is readily apparent, given the documentation of greatest hyperprolactinemia in this circumstance (Table 1, p. 21).

As noted in the amendment dated July 24, 2007, support for the current language of claim 1 can be found in the specification at page 24, lines 6-8. Further support of the general intent of the claimed invention can be found throughout the text of Examples 1-4. All of this material was present in the provisional patent application as filed on July 8, 2003 (see page 17, lines 27-28, of the provisional application for support for the amendment to claim 1, and pages 2-52 for the Examples). Based on the extensive examples detailing the adverse effects of high dose atypical antipsychotic treatment for A1+ patients and the comparison to the drug response of A1- patients, it would have been apparent to one skilled in the art that the claim language recited previous to the July 24, 2007 amendment contained a clerical error that was corrected by this amendment.

Accordingly, Applicants' possession of the invention as currently claimed was supported by the application as originally filed and the amendment dated July 24, 2007 does not introduce new matter. Reconsideration is respectfully requested.

V. Rejection Under 35 U.S.C. §101

At Pages 3-4 of the Office Action, claims 1, 2, 5, and 6, are rejected under 35 U.S.C. § 101 because the claims allegedly do not constitute statutory subject matter.

The Applicants have amended claim 1 to clarify the language noted in the Office Action. Specifically, the step of "determining whether the patient's DRD2 genotype is Taq1A allele positive (A1+) or Taq1A allele negative (A1-)" has been clarified to explicitly require "genotyping" a specimen obtained from the patient.

Withdrawal of the rejection for failure to recite statutory subject matter is respectfully requested.

VI. Rejections Under 35 U.S.C. §103

At pages 5-8 of the Office Action, claims 1, 2, and 5 were rejected under 35 U.S.C. §103(a) as unpatentable over Suzuki et al., *Pharmacogenetics* (10)4:335-341 (2001) (hereinafter "Suzuki #1"), in view of Suzuki et al., *Am. J. Psychiatry* 158(10):1714-1716 (2001) (hereinafter "Suzuki #2"), and Turrone et al., *Am. J. Psychiatry* 159(1):133-135 (2002). At page 8 of the Office Action, claims 1, 2, 5, and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki #1, Suzuki #2 and Turrone, as applied to claims 1, 2, and 5 above,

and further view of Bourin et al., *CNS Drug Reviews* 7(1):25-47 (2001). The Applicants respectfully traverse these rejections because the cited references fail to teach or suggest all elements of Applicants' claimed invention. Accordingly, the rejection under 35 U.S.C. § 103(a) should be reconsidered and withdrawn.

A. The Claimed Invention

Claim 1 recites a method of identifying a candidate psychiatric patient for treatment with atypical antipsychotic or antidepressant medication that acts at a D2 dopamine receptor (DRD2) or influences D2 dopamine receptor density. The preamble of claim 1 has been amended to explicitly recite "atypical antipsychotic or antidepressant" medication, to clarify that the invention relates to the challenge of prescribing this class of medications, given the variability in their binding strength and in patient response (see para. 0049 at p. 16 of specification). The method comprises determining the patient's DRD2 genotype at the Taq1A allele by genotyping a specimen obtained from the patient.

The invention identifies the A1+ genotype as indicative of a candidate for treatment with low dose DRD2 binding atypical antipsychotics and/or SSRIs. Claim 1 has been further amended to specify that A1+ patients are candidates for treatment with low dose DRD2 binding **atypical** antipsychotics. A1- patients are candidates for treatment with high dose D2 dopamine receptor binding anti-psychotics or alternative antidepressant. This method of identifying candidate patients is based on a variety of studies performed by the inventors and reported in the Examples portion of the specification. Example 1 (pp. 8-14) demonstrates the relationship between A1 allelic status and susceptibility to extrapyramidal effects in response to treatment with the atypical, high binding medication risperidone. Example 2 (pp. 14-24) shows the elevated prolactin response is much worse for A1+ patients treated with the low binding atypical antipsychotic clozapine. Example 3 (pp. 25-35) shows that A1+ patients suffering from PTSD respond well to the SSRI paroxetine, while A1- patients often had adverse reactions to this medication. Example 4 (pp. 35-50) shows comorbid psychopathology in PTSD with A1+ combat veterans.

The claimed invention is therefore based on a wealth of new information provided by the inventors' studies described in Examples 1-4. This new information establishes that A1+ allelic status is associated with greater adverse effects when treated with high dose atypical antipsychotics (Examples 1 & 2) and with therapeutic efficacy when treated with SSRIs (Example 3). A1- patients were shown to respond better to higher doses of DRD2 binding antipsychotics and to fail to show a reduction in symptoms upon SSRI treatment.

B. **The Cited References Do Not Teach or Suggest the Claimed Invention**

The Suzuki #1 and #2 references cited in the Office Action do not teach a method of identifying a candidate psychiatric patient for treatment with **atypical** antipsychotic or antidepressant medication. As noted in the Office Action at page 7, the medication used in the Suzuki references, nemonapride, is a **typical** antipsychotic that binds highly with DRD2 (Seeman, 2002, W. Can. J. Psychiatry, 47(1):29-35, see Table 1 at p. 34; of record per Information Disclosure Statement filed September 6, 2006). In fact, the Office Action (at page 7) states that Suzuki #1 teaches that nemonapride is substantially more effective in treating A1+ patients than A1- patients.

As acknowledged in Applicants' specification (para. 0050 at p. 16), it was previously known that the typical antipsychotic nemonapride is associated with significantly elevated prolactin in A1+ female schizophrenic patients. It was not known prior to Applicants' studies, however, whether there was an association between A1 allelic status and response to the wide variety of antipsychotic agents as well as to SSRIs, and whether any such association would be found independent of gender. The results of these studies could not be predicted, given the variety of patient responses to identical medication at a given dose, the variety of DRD2 binding affinities of the various atypical antipsychotics, and the lack of correlation between prolactin levels and D2 occupancy (see, for example, "Introduction" section of Example 2, at pages 15-17 of specification).

The teachings of Turrone and/or Bourin do not compensate for the gap between the teachings of Suzuki #1 & #2 and Applicants' claimed invention. Turrone, by providing data on prolactin levels of 18 male patients in response to various atypical antipsychotic medications, does not provide guidance to the skilled artisan on determining which patients would be candidates for low dose treatment and which could be well-served by high dose treatment, nor can the teachings of the Suzuki references provide the missing guidance. Bourin, describing paroxetine as an SSRI that lacks affinity for D2 dopamine receptors, does not address the identification of which patients would be candidates for SSRI treatment as a function of Taq1A allelic status.

The combination of these references teaches that female A1+ patients respond better to the typical antipsychotic nemonapride and are at greater risk than A1- patients of neuroleptic malignant syndrome with this treatment (Suzuki #1 & #2), that a small sample of male patients of unknown A1 genotype show higher levels of prolactin in response to risperidone as compared to other atypical antipsychotic medications, and that paroxetine does not bind D2

dopamine receptors. This combination of information does not provide the skilled person with the motivation or guidance to identify which patients will benefit from low dose treatment with atypical antipsychotics or SSRIs and which will benefit from high dose antipsychotic or alternative antidepressant medication.

Accordingly, the rejection of claims 1, 2, 5 and 6 as obvious over the cited references is improper and withdrawal of this rejection is respectfully requested.

VII. Conclusion

In view of the above, it is submitted that this application is now in good order for allowance and such allowance is respectfully solicited. Should the Examiner believe minor matters still remain that can be resolved in a telephone interview, the Examiner is urged to call Applicants' undersigned attorney.

Respectfully submitted,

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